CERTIFICATE OF ELECTRONIC SUBMISSION
January 29, 2007

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Rosenblum *et al.*	Group Art Unit: 1643
Serial No.: 09/320,156	Examiner: Canella, K.A.
Filed: May 26, 1999	Atty. Dkt. No.: CLFR:092US
For: IMMUNOTOXINS DIRECTED AGAINST C-ERBB2 (HER-2/NEU) RELATED SURFACE ANTIGENS	

REPLY BRIEF

MS APPEAL BRIEF
Commissioner for Patents
P. O. Box 1450
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Commissioner:

Appellants hereby submit this Reply Brief to the Board of Patent Appeals and Interferences in response to the Examiner's Answer dated December 1, 2006.

It is believed that no fees are due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski Deposit Account No. 50-1212/CLFR:092US.

Appellants herewith file their reply to the Examiner's Answer dated December 1, 2006.

I. Rejection of Claims 15 and 19 as Obvious Over King et al. ("King") in view of Rosenblum et al. ("Rosenblum")

Claims 15 and 19 are directed to a composition comprising a conjugate of TNF to a ***single chain*** antibody specific for c-erbB-2 protein, and specifies a particular single chain anti-c-erbB-2 antibody designated "scFv-23". The preparation and characterization of this unique single chain antibody construct is described in examples 30 through 36 of the Appellant's specification. Notably, the scFv-23 single chain antibody incorporates a specific ***12 amino acid "212" linker***, the structure and sequence of which is shown in Figures 9A and B.

King is distinguishable and cannot give rise to a "*prima facie*" case of obviousness, for at least the following reasons:

- With respect to claims 15 and 19, King relates to a ***different*** single-chain antibody directed to c-erbB-2. We know this at least because at col. 19, lines 20-21, of King it is stated that the King e23 scFv construct incorporates a 14 amino acid linker, whereas, as noted above, Appellants construct incorporates a different amino acid linker. King is thus directed to a ***different*** scFv construct than that embraced by claims 15 and 19, and there is no art relied upon to bridge that difference.
- King generically refers to the use of a "cytotoxic moiety" and lists various toxins, drugs and radionuclides as examples – notably, the only cytotoxic proteins in this list are toxins. Indeed, King fails to teach or suggest the use of proteins other than plant or bacterial toxins that are inhibitors of protein synthesis, such as Pseudomonas exotoxin, diptheria toxin, ricin and abrin. Col. 8, lines 51-53; col. 10, lines 14-22. No mention is made or suggested to use cytokines for this purpose, and specifically there is no suggestion to prepare TNF conjugates.

- In that, with respect to proteins, King teaches only the use of inhibitors of protein synthesis, King cannot be said to suggest proteins that are not inhibitors of protein synthesis. TNF is not a protein toxin and is not an inhibitor of protein synthesis. See general discussion in Rosenblum, col. 2, page 21. Thus, one of skill would not be motivated from King to look to the use of protein effectors that are not toxin inhibitors of protein synthesis.

Rosenblum fails to provide the missing motivation to use a TNF ligand in the single chain anti-c-erbB-2 construct of King, for at least the following reasons:

- Rosenblum very clearly teaches the use of a TNF ligand only in the context of a ***full-length***, ***ZME-018*** antibody. Both of these differences are important. For example, it is clear that Rosenblum, on its face, fails to provide any suggestion to couple TNF to anything other than a full length antibody, and particularly, a full-length ***murine*** ZME-018 antibody.
- Murine ZME-018 is said to be melanoma specific and recognizes a 240 kD antigen – an entirely different antigen from that recognized by anti-c-erbB-2. Rosenblum teaches that this particular murine antibody is special in its ability to present TNF to the TNF receptor, postulating that it may either "hold TNF-α at the cell membrane in proximity to the TNF-α receptor and, thus, result in improved recognition of the TNF-α ligand by the TNF receptor." Page 25, column 2, Discussion. Alternatively, Rosenblum postulates that the ZME-018 murine antibody promotes an "interaction of the ZME-TNF conjugate with the TNF-α receptor may differ from that of TNF-α alone and may modulate or interfere with the nominal cellular processing of TNF-α receptor-ligand complex." *Id.* In other words, one of skill reading Rosenblum would most certainly conclude that it is the unique use of a full length murine ZME-018 antibody to deliver TNF that makes the construct useful to kill tumor cells.

- There is no teaching in Rosenblum to use any antibody other than the full length murine ZME-018, and no suggestion that any other antibody would have the property that Rosenblum postulates are required – such as binding in appropriate proximity to the TNF receptor.

Thus, for the foregoing reasons, neither Rosenblum nor King suggests that a single-chain, anti c-erbB-2 construct would provide a proper and useful targeting for TNF and would provide an appropriate binding site on the cell surface to render the TNF useful in killing c-erbB-2 positive cancer cells. The Examiner's principal response to this is that one of skill in the art would understand that single chain antibodies are easier to produce than a whole antibody. While we question this statement as apparently based on the Examiner's personal knowledge and not properly validated on this record, we would note that this statement does not address the fact that Rosenblum postulates, as noted above, that the ability of TNF to act on particular cells is a function of the particular antibody, including binding site proximity to the cellular TNF receptor. Rosenblum teaches only a full-length antibody – one that specifically recognizes the 240 kD ZME-018 antigen – and teaches away from the conclusion that other antibodies will work.

II. Rejection of Claims 15-17 and 19 King and Rosenblum, further in view of Gillies

Appellants incorporate the remarks set forth above with respect to King and Rosenblum, and will focus here on Gillies, which we contend fails to provide the missing teachings discussed above and would, in fact, lead the skilled artisan still further away from the claimed invention.

Gillies discloses fusion proteins of cytokines, including TNF, to ***full-length*** antibodies, and, in particular, generally specifies that the cytokine should be attached to "heavy chain" of the full-length antibody. See col. 2, lines 10, 39-40, 55-56; moreover all of the claims are limited to attachment to the Ig heavy chain. Indeed, Figure 1 teaches that the cytokine is to be attached to the ***carboxy*** terminus of the heavy chain (see elements 2 and 4 of Figure 1), which is far removed from

the variable regions at the opposite end of the full length Ig molecule. Importantly, single chain antibodies do not have a carboxy terminal of a heavy chain and do not have a "heavy chain" at all. Specification, Figure 9, showing that single chain antibodies are composed only of a V_L combined with a V_H region, and thus do not have a heavy chain, which is composed of the V_H and C_H regions together in a single molecule.

Furthermore, Gillies teaches that the combination of a cytokine with an antibody molecule is inherently unpredictable:

> A way to deliver the lymphokine to a specific site in vivo is to conjugate it to an immunoglobulin specific for the site. ***However, the fusion of protein domains to the carboxy-termini of immunoglobulin chains or fragments can have unexpected consequences for the activities of both the protein to be fused and the immunoglobulin, particularly as far as antigen binding, assembly and effector functions are concerned.*** For example, the desired biological functions of the individual proteins may not be maintained in the final product.

Gillies, col. 1, lines 41-50 (emphasis ours).

Thus, Gillies fully supports and is consistent with the teachings of Rosenblum that the delivery of TNF using antibodies is generally unpredictable. Both references teach the use of full length antibodies, suggesting that such is one way to minimize the unpredictability. Indeed, Gillies teaches to use a structure not found on single chain antibodies and Rosenblum teaches to use a specific ZME-018 antibody.

Thus, both Rosenblum and Gillies point us away from using a single-chain antibody to deliver TNF. Of the references relied on by the Examiner, only King provides a teaching of a single chain antibody, but, with respect to the delivery of proteins, its teaching is uniquely limited to

delivery of toxins. Such a teaching is, as confirmed by Rosenblum, inapplicable to TNF, in which context the secondary references teach the importance of using specific, full-length antibodies, and particularly those having a "heavy chain" which is absent in single chain antibodies.

For all of the foregoing reasons, the Board is requested to reverse the Examiner's conclusion of obviousness.

Respectfully submitted,

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